

Claims:

1. An isolated polypeptide complex comprising a pleiotrophin protein and a pleiotrophin-receptor protein.
2. The complex of claim 1 wherein the pleiotrophin protein is selected from the group consisting of PTN, miple, midkine, recombinant pleiotrophin and combinations thereof.
3. The complex of claim 1 wherein the pleiotrophin-receptor protein is selected from the group consisting of ALK, LTK, recombinant pleiotrophin-receptor protein and combinations thereof.
4. The complex of claim 1 wherein the pleiotrophin protein is bound to the pleiotrophin-receptor protein.
5. The complex of claim 1 wherein the pleiotrophin protein is of human origin, and the pleiotrophin-receptor protein is of non-human origin.
6. The complex of claim 1 wherein the pleiotrophin-receptor protein lacks a signal transduction activity.
7. The complex of claim 6 wherein the signal transduction activity is tyrosine kinase activity.
8. The complex of claim 1 wherein the pleiotrophin-receptor protein comprises one or more, but not all portions of a full-length pleiotrophin receptor protein.
9. The complex of claim 8 wherein the one or more regions are selected from the group consisting of an extracellular domain, an intracellular domain, a pleiotrophin binding site, a growth factor binding site, a mitogenic factor binding site, an antigenic domain, tyrosine kinase, a heparin binding site, a glycosylated domain, a non-glycosylated domain, a signaling domain, a functional domain, a conserved domain, a transmembrane domain, and combinations thereof.
10. A recombinant polypeptide comprising one or more, but not all regions of a full-length pleiotrophin receptor protein.
11. The polypeptide of claim 10 wherein the one or more regions are selected from the group consisting of an extracellular domain, an intracellular domain, a pleiotrophin binding site, a growth factor binding site, a mitogenic factor binding site, an antigenic domain, tyrosine kinase, a heparin binding site, a glycosylated domain, a non-glycosylated domain, a signaling domain, a functional domain, a conserved domain, a transmembrane domain, and combinations thereof.
12. The polypeptide of claim 10 which is antigenic.

13. The polypeptide of claim 10 which contains anti-angiogenic activity.
14. The polypeptide of claim 10 which induces apoptosis.
15. The polypeptide of claim 10 which contains anti-motogenic activity.
16. The polypeptide of claim 10 which contains anti-mitogenic activity.
17. The polypeptide of claim 10 which contains anti-cell proliferative activity.
18. A nucleic acid which encodes the polypeptide of claim 10.
19. The nucleic acid of claim 18 wherein the encoded polypeptide is functionally or antigenically active.
20. A vector containing the nucleic acid of claim 18.
21. A composition comprising the polypeptide of claim 10.
22. The composition of claim 21 wherein the polypeptide contains the pleiotrophin-binding site.
23. The composition of claim 22 wherein the polypeptide is a peptido-mimetic.
24. A recombinant polypeptide comprising one or more, but not all regions of a full-length pleiotrophin protein.
25. The polypeptide of claim 24 which comprises a pleiotrophin receptor binding portion, which binds but does not activate a pleiotrophin-receptor protein.
26. A nucleic acid which encodes the polypeptide of claim 24.
27. The nucleic acid of claim 26 wherein the encoded polypeptide is functionally or antigenically active.
28. A vector containing the nucleic acid of claim 26.
29. A composition comprising the polypeptide of claim 24.
30. The composition of claim 29 further comprising a pharmaceutically acceptable carrier selected from the group consisting of water, oils, alcohols, salts, fatty acids, saccharides, polysaccharides and combinations thereof.
31. An antibody which is reactive against a pleiotrophin protein.
32. The antibody of claim 31 wherein the pleiotrophin protein is PTN.
33. The antibody of claim 31 which specifically binds to the pleiotrophin-receptor protein binding site of said pleiotrophin protein.

34. The antibody of claim 31 which is selected from the group consisting of IgG, IgM, Fab fragments, Fv fragments, recombinant antibodies and humanized antibodies.
35. The antibody of claim 31 which is a monoclonal antibody.
36. A hybridoma which produces the monoclonal antibody of claim 35.
37. An antibody which is reactive against a pleiotrophin-receptor protein.
38. The antibody of claim 37 wherein the pleiotrophin-receptor protein is ALK.
39. The antibody of claim 37 which is specifically reactive against a pleiotrophin-binding site of said pleiotrophin-receptor protein.
40. The antibody of claim 39 wherein the pleiotrophin-binding site comprises amino acid sequence positions 368-447.
41. The antibody of claim 39 wherein the pleiotrophin-binding site comprises amino acid sequence positions 391-401.
42. The antibody of claim 37 which blocks activation of said pleiotrophin-receptor protein.
43. The antibody of claim 37 which activates said pleiotrophin-receptor protein.
44. The antibody of claim 37 which is selected from the group consisting of IgG, IgM, Fab fragments, Fv fragments, recombinant antibodies and fragments, synthetic antibodies and fragments, and humanized antibodies and fragments.
45. The antibody of claim 37 which is a monoclonal antibody.
46. A hybridoma which produces the monoclonal antibody of claim 45.
47. A kit comprising a pleiotrophin-binding region of a pleiotrophin-receptor protein and a pleiotrophin-receptor binding region of a pleiotrophin protein, for screening a substance for an ability to block interaction between pleiotrophin and pleiotrophin receptor.
48. The kit of claim 47 wherein the pleiotrophin-binding region comprises amino acid positions 391-401 of ALK.
49. The kit of claim 47 wherein the substance is selected from the group consisting of antibodies, additional pleiotrophin proteins, additional pleiotrophin-receptor proteins, drugs, anti-angiogenic substances, anti-proliferative substances, anti-motogenic substances, anti-metastatic substances, apoptotic substances, anti-tumorigenic substances, anti-neoplastic substances, biologically active substances and combinations thereof.

50. A method for evaluating an activity of a substance comprising:
incubating an amount of the substance with at least interacting portions of a pleiotrophin protein and a pleiotrophin receptor protein;
determining a first measure of interaction between the interacting portions;
comparing the first measure of interaction with a second measure of interaction determined with a different amount of the substance; and
evaluating the activity of the substance.
51. The method of claim 50 wherein incubating comprises contacting the substance with the interacting portions for a predetermined period of time and at a predetermined temperature.
52. The method of claim 50 wherein the predetermined period of time is between one second and ten days.
53. The method of claim 50 wherein the predetermined temperature is between 4°C and 37°C.
54. The method of claim 50 wherein the amount of substance is a physiologically effective amount.
55. The method of claim 50 wherein the different amount of substance is selected from the group consisting of no substance, ten percent of a physiologically effective amount, twenty percent of a physiologically effective amount, fifty percent of a physiologically effective amount, a physiologically effective amount, two times a physiologically effective amount and ten times a physiologically effective amount.
56. The method of claim 50 wherein the substance is selected from the group consisting of antibodies, additional pleiotrophin proteins, additional pleiotrophin-receptor proteins, drugs, anti-angiogenic substances, anti-proliferative and proliferative substances, anti-motogenic and motogenic substances, anti-metastatic substances, apoptotic substances, anti-tumorigenic substances, anti-neoplastic substances, biologically active substances and combinations thereof.
57. The method of claim 50 wherein the activity is selected from the group consisting of anti-angiogenic activity, anti-proliferative and proliferative activity, anti-motogenic and motogenic activity, anti-metastatic activity, apoptotic activity, anti-tumorigenic activity, anti-neoplastic activity, and combinations thereof.

58. The method of claim 50 further comprising comparing interactions that occur and varying incubation times.

✓ 59. A method for evaluating an activity of a substance comprising:

incubating the substance with at least interacting portions of a pleiotrophin protein and a pleiotrophin receptor protein for a first period of time;

determining a first measure of interaction between the interacting portions;

incubating the substance with the at least the interacting portions for a second period of time;

determining a second measure of interaction between the interacting portions;

comparing the first measure of interaction with the second measure of interaction; and

evaluating the activity of the substance.

✓ 60. A method for treating a patient comprising administering to said patient a therapeutically effective dose of a composition comprising a pleiotrophin-receptor protein or fragment thereof.

61. The method of claim 60 wherein the patient is a human.

62. The method of claim 60 wherein administering comprises direct injection of the composition.

63. The method of claim 60 wherein the therapeutically effective dose is that amount which will bind to at least half of free pleiotrophin of said patient.

64. The method of claim 60 wherein the fragment comprises a pleiotrophin-binding portion of said pleiotrophin-receptor protein.

65. The method of claim 60 wherein treating stimulates a cell proliferation.

66. The method of claim 65 wherein the cell proliferation comprises creation and growth of blood vessels.

67. The method of claim 60 wherein treating prevents a cell proliferation.

68. The method of claim 67 wherein the cell proliferation is a tumor or a metastasis.

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Table 1

Expression of ALK mRNA in different cell lines in comparison to their response to PTN.

<u>Cell Line</u>	<u>Expression of ALK mRNA</u>	<u>Growth in Response to PTN</u>
endothelial: HUVEC	+	+
fibroblast: NIH3T3	+	+
adrenal carcinoma: SW-13	+	+
pancreatic cancer: Colo357	+	+
squamous cell: ME-180	+	+
glioblastoma: U87	+	+
breast cancer: MDA-MB 231	-	-
choriocarcinoma: JEG-3	-	-
hematopoietic cells: 32D	-	-

RT-PCR was used to detect mRNA expression of ALK in cells in culture. Products from the reaction were separated by gel electrophoresis and blotted onto nitrocellulose. Specific PCR products were visualized by hybridization with a radiolabeled, bested oligonucleotide. Response to PTN was assessed as mitogenesis or soft agar colony formation.

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